Drug resistance: The next AIDS crisis
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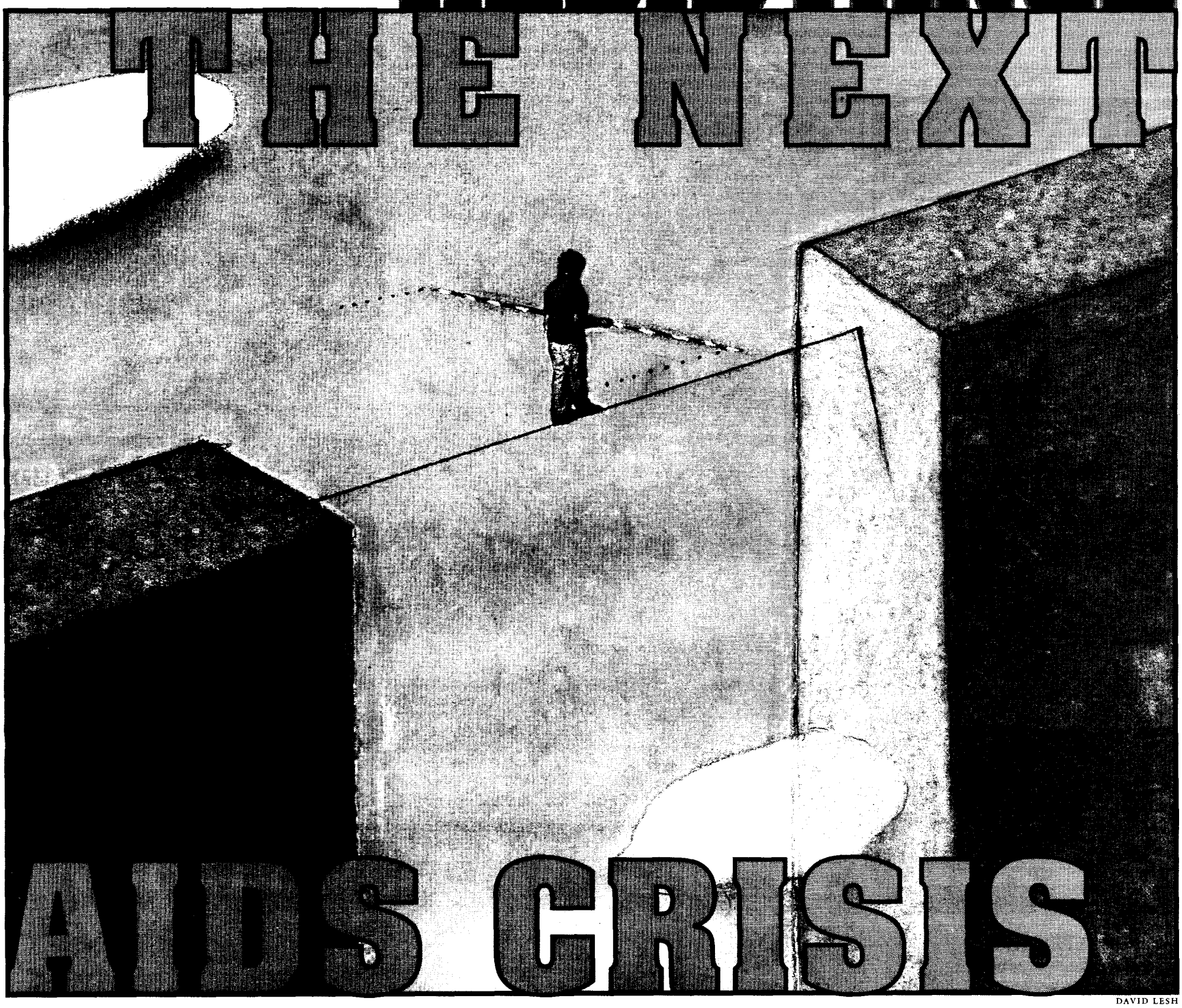
The Village Voice; Jul 9, 1996; 41, 28; ProQuest
pg. 15

DRUG RESISTANCE: THE NEXT AIDS CRISIS



DAVID LESH

By **Mark SCHOOFS**

The 11th International Conference on AIDS, which will draw thousands of researchers and reporters to Vancouver next week, promises to be a festival of optimism. Studies will confirm that at least five new drugs attack HIV with astonishing ferocity. When taken together with two medications from the old armory of AZT and its cousins, these "triple-combination therapies" suppress HIV so effectively in most patients that the virus cannot be detected in their blood. Even more encouraging, several of these three-drug regimens have kept HIV pinned down for a year and, in a handful of patients, for even longer.

But these hopeful findings may blind experts to an urgent problem. Unless the new drugs are taken according to a strict regimen, HIV can mutate into a strain that is resistant to all three drugs. And this new strain could also be resistant to drugs the patient *has never taken*, because of a phenomenon called "cross-resistance," in which the mutations a virus makes to evade one drug enable it to elude others. In such cases, the patient might lose his chance for any effective treatment.

The new drugs—especially a type called "protease inhibitors"—are the culmination of 15 years and billions of dollars in AIDS research. Missing out on their benefit would be tragic for infected individuals. But there is also the specter of a public-health calamity. Currently, about 10 per cent of newly infected people contract a virus that is resistant to AZT. In the future, people could get infected with a strain of HIV that is resistant to several drugs, leaving them with few or no treatment options.

"All our enthusiasm has to be tempered by one big issue," says Dr. Julio Montaner, cochair of the Vancouver conference, "and that is the ability of patients to take the treatments. I don't think that should be underestimated; it's a major challenge in our ability to treat HIV effectively." Like many other AIDS researchers, Montaner draws an analogy with tuberculosis, which has mutated into strains that are resistant to most antibiotics. "TB is coming back all over the world," he says, "because compliance with TB treatments is not easy for patients." He warns that the new HIV regimens are even harder to take and must be administered for much longer periods of time, perhaps for life.

HIV is a master of mutation. It multiplies like a bionic bunny, producing a new generation every two days. In an untreated person, up to 10 billion new viruses are created daily, many with slight variations. When a drug attacks this population of HIV, the variants it can't stop from replicating continue to multiply. These are the resistant strains.

Why would three drugs be better than one at preventing resistance? "If you ask HIV to jump one hurdle at a time, it has no trouble," explains Dr. David Ho, a leading AIDS researcher. "But if you stack the hurdles on top of one another, the virus finds it very difficult to jump them all at once."

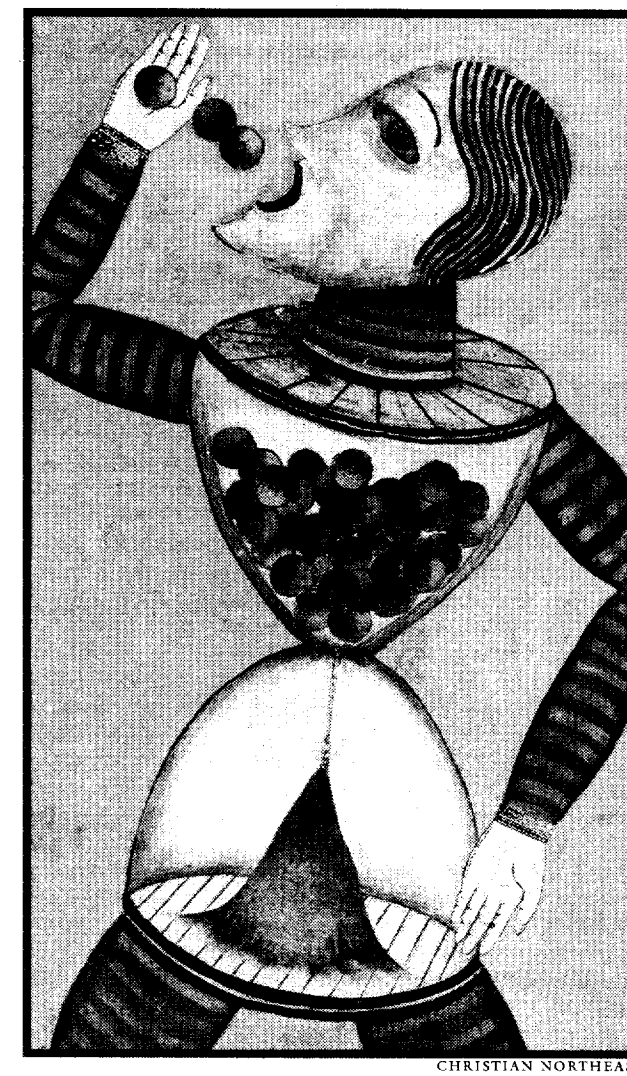
Resistance is a complex process. Some strains are able to overcome low concentrations of a drug, but higher doses can keep them in check. And even if a virus is fully resistant, the mutations that allow it to survive often hobble it, slowing down the replication cycle. If a virus does get over the hurdle, its successive generations will become stronger, able to reproduce faster and resist higher doses of the drug. "Once resistance selection begins to occur," says Dr. Emilio Emini, Merck's chief AIDS researcher, "it's inexorable. You can't stop it."

So the hurdle must never be lowered. This means patients must take their pills on a tight schedule. The old AZT-class of drugs stayed in the body for up to two days; if a patient missed a dose, the medicine was probably still working against the virus. But the new drugs pass out of the body very quickly. If a patient misses a dose, HIV will be free to replicate.

Forgetting one dose probably won't give HIV a chance to become resistant. But no one knows how much slack there is: Missing several doses a week for a month might do it. "We're used to skipping a few days when we're not feeling well, we're used to changing doses and to taking drug holidays," says Spencer Cox, a longtime AIDS activist who is currently on triple therapy. "But with these drugs, there's not much room for noncompliance."

Other factors make sticking to the schedule difficult. One protease inhibitor, manufactured by Abbott, has to be kept refrigerated, which can make traveling—or simply going on a picnic—tricky. Merck's drug must be taken three times a day on an empty stomach. If the drug is ingested too close to a meal, not enough will get absorbed into the bloodstream and the hurdle will be that much lower.

Roche's drug, in its current formulation, is not absorbed well by the body, period. Many doctors and activists believe taking this drug is the same as taking too low a dose, which can actually speed up the development of resistance. The company denies this, but it is feverishly working to get an improved formulation licensed by the Food and Drug Administration. It is also exploring a serendipitous synergy with Abbott's drug:



CHRISTIAN NORTHEAST

Taking the two together improves absorption, and the combination may be more powerful than either drug alone.

Then there are the side effects. Abbott's new drug, ritonavir, seems to cause the worst reactions, though they usually last for only two to four weeks. Cox, who is on ritonavir, describes the symptoms: "I had lots of diarrhea. My skin was very sensitive; it hurt to comb my hair, and the elastic on my underwear hurt. Sometimes I would get a bit dizzy and disoriented. My lips and mouth went numb, and I almost completely lost my sense of taste." He adds wryly, "I redid the entire apartment in shag carpeting."

Merck's drug, indinavir, can also cause diarrhea and nausea. Roche's drug, saquinavir, is tolerated best, but it too can cause side effects. And no one knows if the drugs will harm people years down the road, especially in combination. "These are new chemicals we're putting into human beings," says Ho.

Another problem: There are dozens of drugs that might cause dangerous, even fatal, reactions if taken with protease inhibitors. Many doctors are not familiar with all these cross-reactions, or they discount the risk because it has not been been proven. "I've had a doctor and a dentist try to prescribe drugs with potentially lethal interactions," says Cox, "and I'm supposedly seeing the best in the city." A severe drug interaction could force patients to abandon their anti-HIV drugs for a while, which could open an opportunity for the virus to develop resistance.

Finally, no one knows how long patients will have to stick to this demanding regimen. It is conceivable that triple therapy could eliminate HIV not just from the blood but from the entire body. To put it plainly, these medicines might cure some people. But even if this turns out to be true, no one knows how long it would take. If the virus is absent from the blood for years, it might still lurk in the lymph nodes, the brain, or other "sanctuary sites." One patient taking Abbott's drug had virus-free blood for 18 months, but a recent biopsy of his lymph nodes turned up HIV that was capable of replicating. Curative therapy, if it were even possible, would take years.

The hopeful news about AIDS obscures an urgent problem. Unless the new drugs are taken on a strict schedule, HIV can become resistant to them.

In the much more likely event that HIV cannot be eradicated, just kept at bay, patients would have to stay on the drugs for as long as they kept working—possibly for life.

No one knows exactly how many people are already on the new drugs. The number is estimated at at between 30,000 and 40,000—a large group, but only about 5 per cent of Americans infected with HIV. Most of these pioneers have generous insurance policies and doctors on the cutting edge of AIDS therapies. Informed, motivated, and well cared for, these patients are the most likely to adhere to a complicated regimen.

But AIDS is growing fastest among those least likely to stick to the new therapy: drug addicts, the homeless, and people lacking adequate medical care. In what Ronald Johnson, Mayor Giuliani's AIDS policy chief, calls "a perverse blessing," these people have had virtually no access to the new drugs. But that is about to change.

The federal government recently advised all state medicaid programs that they must pay for protease inhibitors, which start at about $5000 per year. (Triple therapy starts at about $10,000.) Just last week, Governor Pataki announced that New York State's AIDS Drug Assistance Program, which subsidizes AIDS medicine, will cover the new drugs. While Johnson favors making the new drugs affordable for all patients, he also fears that without a strong public-health effort, expanding access will "greatly enhance" the potential for misuse of the drugs. As a consequence, drug resistance could leave the most vulnerable people with AIDS unable to benefit from state-of-the-art therapies.

"This would be the most graphic example yet of our two-tiered health care system," says Dr. Joseph O'Neill, director of the AIDS program at the federal Health Resources and Services Administration. "Access means not only that you can get the drug but that you have an environment in which you have a fighting chance to take it appropriately."

To give all patients a fighting chance, scientists and activists have been shouting from the rooftops, emphasizing the parallel with tuberculosis. To control this situation, you have to use "the same mechanisms" that curtailed TB, says Dr. Emini of Merck. When the epidemic of drug-resistant tuberculosis emerged five years ago, largely among this same population, patients who were judged incapable of taking their medicine as directed were "directly observed"—and a few recalcitrant patients were confined. The practice of watching people actually swallow their pills proved remarkably effective, but it is an expensive and intrusive last resort. It was introduced because TB bacteria, unlike HIV, can be spread by breathing. So public-health officials agree that directly observed therapy is unlikely to be deployed.

Instead, counseling, case management, and extensive education will be necessary. But public-health officials have been slow to respond. The *Voice* faxed a description of the threat posed by drug-resistant HIV to various authorities and asked them what steps they were taking.

"We believe it is too soon to say there will definitely be a problem with multiple-drug-resistant HIV," replied a spokesperson for Barbara DuBuono, New York State Commissioner of Health. "If we see signs of it, then we will take action." New York City Health Commissioner Margaret Hamburg said, "We have to be very, very aggressive about both physician and patient education." But Hamburg acknowledged that the only concrete action underway was a

special issue of a newsletter the health department sends to doctors. And a spokesperson for the American Medical Association responded: "We used to have an HIV virologist, but we don't right now. That's the only person who would address something like that."

The strongest action is being taken by Eric Goosby, director of AIDS policy for the Department of Health and Human Services. A physician who still sees AIDS patients, he is overseeing the development of a comprehensive plan to deal with issues created by the new drugs. To encourage patient compliance, he expects to promote "regular ongoing assessment that would escalate up to, but probably stop short of, directly observed therapy." But Goosby will not say how much money he is requesting for the effort, because the plan will not be submitted to HHS secretary Donna Shalala until mid July.

By that time, seven months will have elapsed since the first protease inhibitor hit the market, and many thousands will have embarked on protease therapy. The new drugs offer the best hope people with AIDS have ever had. Indeed, the threat of resistance is so dire precisely because the treatment is so promising. To squander this opportunity would be heartbreaking—and scandalous.

"This exposes a huge gap in the medical system," says activist Martin Delaney of Project Inform. "When you finally have a great medication, there's no strategy for delivering it. Every doctor is left on his own." ❖

Research assistance: David Caplan

What They Don't Know Can Hurt You

Call it a confusion of riches. In six months, the number of licensed drugs that attack HIV has almost doubled. But no one knows how best to use them.

In some cases, doctors haven't done their homework. A Gay Men's Health Crisis survey, answered by 40 experienced AIDS physicians, revealed a common practice most researchers believe is a mistake: adding a protease inhibitor to a patient's existing drug regimen. Trouble is, if that patient has been taking the old medications for several months, his or her HIV might have developed resistance. If so, adding the protease inhibitor could "waste" it very quickly, warns prominent AIDS scientist David Ho.

Then there is the general uncertainty about how to take these new drugs. So far, there are only three crude directives: Take them in combination, take them at full strength, and never miss a dose. Beyond this, even the best doctors have to guess.

The most vexing question is when to start. Should patients begin triple therapy early on, or should they save the new drugs until they are on the brink of full-blown AIDS? "There are people whose prognosis will be excellent even without treatment," explains Calvin Cohen, an AIDS physician and researcher. "There are also people who can take ddI"—a drug from the old AZT family—"and be stable. And we know that ddI doesn't blow your wad for the triple therapy. So you could take two pills instead of 21, and in the meantime we just might perfect this treatment."

But proponents of the hit-early-and-hard strategy argue that doctors should intervene as soon as possible, before HIV wreaks progressive, irreversible damage to the immune system. Also, evidence suggests that HIV is less able to develop resistance for the first few months after a person is infected.

Too many patients, the decision to start taking protease inhibitors hinges on another looming unknown: How long can triple therapy suppress HIV? Dr. William Paul, director of the federal government's AIDS research effort, says it is "irresponsible" to claim the new drugs make AIDS a "long-term, manageable illness," like diabetes. But many people are clearly hoping for that—and more. Last month, an elite scientific conference addressed the question, "Can HIV be eradicated from an infected individual?" and a front-page article in *The Wall Street Journal* touted the new combination therapies as "the first glimmerings of a cure."

Anecdotal reports also reveal glimmerings of the limits of the drugs. In some patients triple therapy does not make HIV disappear from the blood, or it reappears after some time. Will such patients live longer than if they had never taken the drugs?

No one knows. Ho, whose three-drug experiments have generated much of the current hope, says this of the new therapy: "Down deep, all of us don't think we quite have it yet."

So this month, Ho will start a small, four-drug trial. But what's needed, according to researchers and activists, are large trials to answer basic questions about combination therapies. The government has not done these studies; pharmaceutical companies say they're doing their part, but activists (and, privately, some researchers) accuse them of slighting clinical testing after their drugs have been licensed.

So, desperate for answers, some activists are looking for new sponsors, and their gaze is increasingly focused on managed-care companies. HMOs have an economic incentive: They don't want to pay for therapies that are not effective.

Nobody thinks any health care institution can do it alone. "This requires a coming together of industry, government, academia, and the community like never before," says David Barr, head of treatment advocacy for GMHC. Even if that proves possible, the trials will take years. In the meantime, people with AIDS must make life-and-death decisions in the dark.

—Mark Schoofs